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Selective oxidations by nitrosating agents Part 1: Oxidations of ketones in concentrated sulfuric acid

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Abstract

Selective oxidations by nitrous acid in aqueous sulfuric acid towards alkyl side chains of enolizable ketones are reported. The conversion reagents–products in different experimental conditions is explored and the reaction path of the compounds involved as intermediates is tested. Side-chain oxidations are particularly successful for substrates with one site or with equivalent sites of oxidation. Thus, 95% of benzoylformic acid from acetophenone and 60% of 1,2-cyclohexanedione from cyclohexanone are obtained at ∼78 and at ∼40% H_2SO_4, respectively. Kinetic (k_{obs}) and thermodynamic (k°) rate constants of acetophenone are also determined, the latter by using the acidity dependence of the rates, the equilibria involving the reacting species and the departure from the ideality of the catalytic acid system. Details of the process between enolizable ketones and electrophilic species in concentrated aqueous acid solutions are discussed.

Keywords: Oxidation; Ketones; NO^+; Acid catalysis

1. Introduction

Selective oxidations of methyl or methylene groups in an α-position to a carbonyl group are known to be viable routes for obtaining α-ketoacids [1]. However, the conversion acetophenone to benzoylformic acid with reagents such as selenium dioxide [2–4], thionyl chloride [5,6], mixtures of nitric and nitrous acids in organic solvents [7], potassium permanganate in potassium hydroxide [8–10], gives the product in low yields together with furazan-2-oxide, phenylglyoxal and benzoic acid.

On the studies of enolizable ketones for the conversion of alkyl to carboxyl groups it was of interest to test the process by nitrous acid in sulfuric acid where reactive ionic species can be easily formed by protonation or protonation–dehydration equilibria of the reagents in suitable acidity ranges. In the present paper ketones with different structure were analyzed and the conversion reagents-products explored in different acidity ranges and experimental conditions.

The reaction rate (k_{1obs}) of acetophenone and the dependence of the rate upon acidity was also determined as well as the rate constants referred to water as standard state (k°). The latter was estimated by using the effective concentrations of the reacting species involved in the acid-base equilibria and the deviations from the ideality of the catalytic acid system. This procedure, according to thermodynamic studies in concentrated aqueous acid mixtures [11–14], allows one to separate the solvent effects involved in the equilibria of the reagents from the solvent effects involved in the kinetic behaviour of the reacting species [15].

The present results have been compared with the ones obtained in the previous studies of side chain detritiation, iodination and bromination of enolizable ketones carried out in aqueous solution of strong acids [16–21]. The details of the process between ketones and electrophilic species in acidic media are of considerable interest in view of an extension of analogous studies over solid acid catalysts.

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2. Experimental

2.1. Materials

The commercially available ketones (Aldrich) were purified by the appropriate procedure. H_2SO_4 95–97% (Riedel de Haen), $NaNO_2$ P.A. (Fluka). Aqueous acid solutions were prepared by diluting concentrated acids and their percentage compositions were measured by automatic potentiometric titration against a standard solution of sodium hydroxide. Separate solutions of ketones and sodium nitrite in sulfuric acid of appropriate concentrations were prepared using weighed samples of solvent and reagents.

2.2. Conversion reagents–products

A typical reaction was carried out by mixing appropriate volumes of solutions containing, respectively, the ketone and sodium nitrite, in titrated aqueous sulfuric acid. The mixtures were kept under stirring in a thermostatted reactor, then poured into water at the end of reaction and analyzed by HPLC. Analogous mixtures, after extraction with dichloromethane, were analysed by GC–MS using an HP5 capillary column. It is noteworthy that, during the course of the reaction evolution of NO_x as has been constantly observed. The concentrations of the reagents were in the range 0.1–0.25 mol l^{-1} for ketones and 0.2–1.5 mol l^{-1} for the oxidant. Extensive decomposition of the nitrosating agent occurs at sulfuric acid concentration lower than 65% since formation of NO^+ is not complete and the initial blue colour of the solutions, due to the N_2O_3, vanishes [22–26]. Under these experimental conditions, difficulty experienced in obtaining a reliable evaluation of the oxidant leads to a lower accuracy of the estimated values. The ketones investigated are in Tables 1–4, together with conversion and yields of the main products obtained after 24 h, unless otherwise

Table 1
Oxidation of $PhCOCH_3$ in H_2SO_4 by HNO_2

H_2SO_4[a] (%)	Ratio[b] reagents	T (°C)	Conversion[c] (%)	Yield (%) PhCOCOOH	Yield (%) PhCOOH	Ratio[d] products	Yield (%) of[e] other compounds
64.1	1:3	25	36.0	6.6	11.6	0.6	17.8
71.9	1:3	25	34.6	7.7	13.3	0.6	13.6
77.4	1:3	25	26.0	3.1	3.4	0.9	19.5
87.2	1:3	25	7.5	0.7	1.8	0.4	5.0
94.0	1:3	25	7.0	1.2	3.2	0.4	2.6
96.0	1:3	25	6.5	1.0	0.9	1.1	4.6
77.1[f]	1:4	25	95	80	10	8	5
44.6	1:6	25	89.1	37.8	12.3	3.1	39.0
56.2	1:6	25	95.4	51.6	11.8	4.4	32.0
64.1	1:6	25	99.5	60.7	10.9	5.6	27.9
70.9	1:6	25	99.0	75.8	12	6.3	11.2
71.9	1:6	25	98.8	81.0	12.8	6.3	5.0
74.1	1:6	25	98.1	84.4	12.3	6.9	1.4
77.1	1:6	25	99.9	93.3	6.2	15	0.4
77.2[g]	1:6	25	99.1	94.0	4.8	19.6	0.3
77.4	1:6	25	97.2	83.9	11.4	7.3	1.9
82.4	1:6	25	69.3	30.3	12.8	2.4	26.2
87.2	1:6	25	28.8	9.0	7.6	1.2	12.2
94.0	1:6	25	9.2	4.8	4.2	1.1	0.2
96.0	1:6	25	8.8	1.8	2.5	0.7	4.5
71.9	1:9	25	99.0	80.0	13.5	5.9	5.5
77.2	1:9	25	99.9	90.0	9.5	9.5	0.4
77.4	1:9	25	99.0	82.0	13.3	6.2	3.7
87.2	1:9	25	35.0	8.5	8.0	1.1	18.5
94.0	1:9	25	10.2	4.5	4.1	1.1	1.6
96.0	1:9	25	9.8	1.5	3.5	0.4	4.8
77.2	1:12	25	99.8	87.8	11.5	7.6	0.5
77.2	1:6	5	94.0	86.1	6.7	12.8	1.2
77.2	1:6	10	99.0	93.9	4.4	21.3	0.7
77.2	1:6	50	98.9	86.7	9.5	9.1	2.7
77.2	1:6	75	99.0	82.8	15.2	5.4	1.0

[a] In AcOH and Ac_2O at 25 °C, by using $NOSO_4H$ as oxidant, conversions of $ArCOCH_3$ = 55% and yields of PhCOCOOH = 9% are observed. Yields of PhCOOH = 30% ca. have also been found.
[b] Ratio of $PhCOCH_3/HNO_2$.
[c] Conversion and yields of products after 24 h analysed by HPLC.
[d] Ratio of ArCOCOOH/ArCOOH.
[e] Not identified products.
[f] Conversion and yields of products after 60 h.
[g] Using ratios $ArCOCH_3$:HNO_2 of 1:1, 1:1.5, 1:2, the conversions and the yields of ArCOCOOH are <10%.

Table 2
Oxidation in H_2SO_4 at 77 wt.% by HNO_2 at 25 °C

Compounds	Conversion[a] (%)	Yield (%)[a] PhCOCOOH	Yield (%)[a] PhCOOH
$ArCOCH_2CH_2CH_3$[b]	>99	30	60
$ArCOCH(CH_3)_2$	>99	<1	98
$ArCOC(CH_3)_3$	2	<1	<1
ArCOAr	2	–	–

[a] Conversion and yields of products after 24 h; ratio ketones:HNO_2 = 1:4.
[b] Propionic and acetic acids have also been detected.

reported. Further experimental details in the oxidation of acetophenone were obtained by using different procedures:

(a) By following the formation of the products during the reaction course. For instance, HPLC analysis of the mixtures at different times shows, besides the starting material and the final products, a number of new compounds. Among them, with the aid of external standards, α-nitroso-acetophenone and phenylglyoxal were identified as reaction intermediates, with decreasing yields as they were converted into the final products.
(b) By isolation and analysis of the main products observed. After extraction with dichloromethane the compounds formed in appreciable amounts, were isolated by fractionation of the organic layers through a chromatographic column and the collected samples analysed by GC–MS. The observed molecular ion peaks indicate that α-dinitroso- and α-trinitroso-acetophenones can be intermediates of the process under the experimental condition employed.
(c) By testing the stability of benzoylformic acid under different experimental conditions. The compound was found to be very stable up to 90% H_2SO_4 with and without addition of an excess of oxidant.
(d) By testing the reaction between acetophenone and nitrosylsulfuric acid in non aqueous solvents. The results obtained in CH_3COOH and $(CH_3CO)_2$ at 25 °C are reported in Table 1.

The experimental trend of a cyclic ketone in strong acidic media is given in Table 4 where the conversion cyclohexanone to 1,2-cyclohexanedione is reported, the latter being the main product expected by a selective mild oxidation of the methylene group [1,27]. Under the experimental conditions adopted, 1,2-cyclohexanedione initially formed reacts afterwards, with a decrease of the yields as increase the time of reaction and/or the acidity of medium. Numerous attempts to detect the reaction intermediates by UV, NMR, GC–MS, using different acidity ranges, ratio of reagents and low temperatures were not successful. The limitations are due to the complex mixture of the products observed at different times, not easy to be identified. Indeed, cyclic α-diketones tend to be strongly hydrated with large effects on keto–enol interconversion, reactivity and stability [28,29].

2.3. Kinetic measurements

The rate constants for the oxidation of acetophenone to benzoylformic acid by nitrous acid in sulfuric acid at 25 °C are reported in Table 5. The kinetic runs were performed by a procedure entirely analogous to that described above. In this case, small amounts of the reacting mixtures were drawn at different times and the samples were analysed by HPLC. Following the variations of both acetophenone and benzoylformic acid, a first order reaction with respect to acetophenone ($\log k_{1obs}$) was observed, in agreement with earlier results obtained in the reaction between acetophenone and electrophilic species carried out in concentrated aqueous acid solutions [16–21].

In the kinetic study, a thermodynamic treatment of the rates was also attempted by taking into account the equilibria of the reacting species, their effective concentrations (i.e. $\log[H^+]$ values of the solvent [13,14], $\log\{[PhC(OH)CH_3]^+/[PhCOCH_3]$ [18,30–32]} and $\log\{[NO^+]/[HONO]\}$ ratios of the reagents [22–26], etc.) and the activity coefficient function (Mc function) of the acidic mixtures [11–14]. The treatment allows one to obtain reaction rates referred to water as standard state ($\log k^\circ$). The

Table 3
Oxidation of benzylacetone in H_2SO_4 at 25 °C

H_2SO_4 (%)	Conversion[a] (%)	Yield (%)[a] PhCHO	Yield (%)[a] PhCOOH	Yield (%)[a] $PhCH_2COOH$	Yield (%)[a] $Ph(CH_2)_2COOH$	Yield (%) of others products[a,b]
31.2	30.2	3.8	2.8	–	–	23.6
41.2	44.1	3.9	3.1	5.9	2.2	29.0
45.0	55.1	4.2	3.2	7.5	5.2	35.0
54.3	98.2	5.2	2.5	17.4	7.5	65.6
55.8	98.6	6.2	2.8	18.5	7.8	63.3
58.1	99.2	6.6	6.5	21.3	11.0	53.8
70.9	99.6	6.8	12.3	30.7	12.3	37.5
71.9	99.2	7.6	15.4	33.2	15.2	27.8
77.4	99.9	50.3	24.8	13.4	6.8	4.6
82.4	99.9	60.5	28.7	4.8	1.0	4.9
87.2	99.9	72.9	13.9	2.8	0.8	9.5
96.0	99.9	27.1	9.2	–	–	63.6

[a] Conversion and yields of products after 48 h; ratio ketone:HNO_2 = 1:6.
[b] Pyruvic acid ($CH_3COCOOH$) has also been detected.

Table 4
Oxidation of cyclohexanone (Cyhex) in H_2SO_4 by HNO_2 at 25 °C

H_2SO_4 (%)	Ratio Cyhex/HNO_2	Conversion[a] (%)	Yield (%)[a,b] 1,2-$C_6H_8(=O)_2$
(A) Acidity dependence of conversions and yields			
H_2O	4	0	0
2	4	20	5
5	4	21	12
10	2.4	16	11
16	2.4	24	23
30	2.4	32	31
31	2.4	33	32
32	2.4	34	33
38	2.4	61	53
40	2.4	75	40
40	3	74	31
40	4	95	35
40	6	99	25
45	2.4	70	31
45	4	81	33
58	2.4	68	15
64	2.4	75	6
72	2.4	90	–
77	2.4	95	–
87	2.4	98	–

H_2SO_4 40%[c]			H_2SO_4 45%[c]		
Time (min)	Conversion[a] (%)	Yield (%)[b] 1,2-$C_6H_8(=O)_2$	Time (min)	Conversion[a] (%)	Yield (%)[b] 1,2-$C_6H_8(=O)_2$
(B) Variation of products with time					
4	91	16	2	75	25
14	91	46	30	77	41
47	91	63	60	77	40
70	92	58	150	78	43
120	93	58	1300	81	33
1260	95	35			

[a] Conversions and yields after 24 h analysed by GC–MS.
[b] 1,2-cyclohexanedione.
[c] [Cyclohexanone]:[HNO_2] = 1:4.

new values have been compared with those estimated by an analogous procedure from the available kinetic data for the reactions between ketones and other electrophilic species in highly acidic media [16–21].

3. Results and discussion

3.1. Analysis of products

It is expected that ketones and nitrous acid in acidic media, are giving reactive ionic species by acid–base interactions between reagents and solvent. From investigations on the equilibria of weak bases, for instance, it is known that acetophenone is half-protonated in 75% H_2SO_4 [$PhCOCH_3 + H^+ \rightleftharpoons [PhC(OH)CH_3]^+$] [18,30–32]. Nitrous acid is half-protonated in 58% H_2SO_4 and is converted into NO^+ by the protonation–dehydration equilibrium ($HONO + H^+ \rightleftharpoons NO^+ + H_2O$) [22–26].

Studies of acidity dependence in sulfuric acid to test the reaction between acetophenone and nitrous acid are now reported in the acidity ranges, ratios of reagents and of the temperatures given in Table 1. The results (conversions and yields) clearly show, that benzoylformic acid (ArCOCOOH) can be easily obtained at 25 °C in the narrow acidity range between 72 and 80% H_2SO_4. In this range, where HNO_2 is almost fully converted into NO^+, the ratios $[PhC(OH)CH_3]^+/[PhCOCH_3]$ appear to be the main factor affecting the results. In contrast, low conversions of the starting material (ca. 55%) and low yields of ArCOCOOH (ca. 9%) are observed with nitrosylsulfuric acid in CH_3COOH or $O(CH_3CO)_2$.

The observed improvement by using a suitable oxidant in strong acidic media suggests that reactive ionic species formed by protonation of the reagents in appropriate acidity ranges lead to an energetically favourite pathway but that the efficiency of the species is related to the acidity of the medium.

Further experimental details of the process dealing with ketones of different structure are reported in Tables 2–4.

In Table 2 typical examples related to substitution of methyl- by *n*-propyl-, isopropyl-, *tert*-butyl-groups are given. As expected, branched alkyl or complex side chains are oxidized with degradation to carboxyl groups. For instance,

benzoic, propionic and acetic acids were detected from butyrophenone ($PhCOCH_2CH_2CH_3$) as fragments of the oxidative process of terminal alkyl group.

Analogous investigations on benzylacetone ($PhCH_2CH_2COCH_3$) with methyl and methylene groups in an α-position to a carbonyl group are reported in Table 3. As compared to acetophenone benzylacetone exhibits a loss of selectivity and different oxidative products as benzoic, phenylacetic, pyruvic and 3-phenylpropionic acids were detected.

The observed experimental trend for the oxidation of cyclohexanone to 1,2-cyclohexanedione is reported in Table 4. The reaction is characterized by a selective oxidation in acidity ranges lower than expected from the protonation equilibrium of the starting ketone (for instance cyclohexanone, similarly to acetone, is half-protonated in 80% H_2SO_4 [33]), but the degree of conversion goes up and the selectivity vanishes as the acid concentration increases. For H_2SO_4 concentrations higher than 40% it comes out that hydration, keto–enol equilibria and reactivity of 1,2-cyclohexanedione are additional factors affecting the main product of reaction with a remarkable influence on selectivity [28,29]. At lower acidity the striking difference between the extent of enolization in cyclohexanone and acetophenone is further emphasized. As well known cyclization appears to favour enolization and accordingly, cycloalkanones contain more enol than do the corresponding open-chain ketones [34–37]. The degree of enolization in the keto–enol mixtures allows the conversion reagents–products with a certain degree of selectivity until equilibria and reactivity of 1,2-cyclohexanedione, already formed, decreases the yields as the medium acidity and/or the reaction time increase.

3.2. Kinetic analysis

Kinetic data obtained by following the variations of acetophenone and benzoylformic acid with time show that the reaction is first order in ketone, with decreasing rate constants ($\log k_{1obs}$) as the acid concentration increases (Table 5A).

Further kinetic details were obtained by using the "effective concentrations" of the solutes involved in the reaction [14,18, 30–32] and the "acidic properties" of sulfuric acid [13,14] on passing from diluted to concentrated aqueous acid solutions. Therefore, we have investigated the protonation of acetophenone whose equilibrium as a weak base (B) in acid solutions (equilibrium 1) is formally described by the thermodynamic Eq. (2) and practically estimated by Eq. (3). In this procedure, the activity coefficient term is evaluated by means of the empirical "activity coefficient function" or "Mc function" [11–14] defined by Eq. (4).

$$B + H^+ \rightleftharpoons BH^+ \quad (1)$$

$$pK_{BH^+} = \log\left(\frac{[BH^+]}{[B]}\right) - \log[H^+] - \log\left(\frac{f_B f_{H^+}}{f_{BH^+}}\right) \quad (2)$$

$$pK_{BH^+} = \log\left(\frac{[BH^+]}{[B]}\right) - \log[H^+] + n_B Mc(i) \quad (3)$$

$$-\log\left(\frac{f_B f_H}{f_{BH^+}}\right) = Mc(i) \quad (4)$$

Table 5
Equilibria and reactivity of acetophenones in aqueous sulfuric acid at 25 °C

H_2SO_4 (%)	$PhCOCH_3$ ($\log k_{1obs}$)[a]	PhCOCOOH ($\log k_{1obs}$)[a]	$PhCOCH_3$ ($\log k_1^*$)[b,c]	PhCOCOOH ($\log k_1^*$)[b,d]
(A) First order rate constants oxidation observed ($\log k_{1obs}$) and effective ($\log k_1^*$)				
64.2	−3.02	−3.24	−2.10	−2.33
68.4	−3.03	−3.28	−2.43	−2.68
70.9	−3.01	−3.24	−2.59	−2.82
75.4	−3.16	−3.32	−2.97	−3.13
77.2	−3.29	−3.36	−3.17	−3.24
80.8	−3.46	−3.50	−3.41	−3.45
82.4	−3.51	−3.58	−3.48	−3.55

Acetophenones	σ[e]	Protonation[f]		Detritiation[g]
		1/2 prot. (%)[f]	pK_{BH^+}	$\log k_1^{\circ}$[h]
(B) Protonation and detitriation of substituted acetophenones in aqueous sulfuric acid at 25 °C				
p-OMe	−0.27	64	−4.1	−0.5
H	0.0	74	−4.6	−0.3
p-Br	0.23	76	−5.0	−0.1
p-NH_3^+	0.60	85	−5.7	0.2
p-NO_2	0.78	88	−6.0	0.4

[a] $[ArCOCH_3] = 0.0422\ mol\ dm^{-3}$; $[HNO_2] = 0.2582\ mol\ dm^{-3}$.
[b] $\log k_1^* = \log\{k_{1obs}(1 + [B]/[BH^+])\}$.
[c] Plot of $\log k_1^*$ vs. Mc (intercept $= \log k_1^{\circ} = -0.3$, slope = 0.51).
[d] Plot of $\log k_1^*$ vs. Mc (intercept $= \log k_1^{\circ} = -0.3$, slope = 0.55).
[e] σ = constants of substituents.
[f] Half protonation data from [18,30–32].
[g] Data from [18].
[h] ($\log k_1^{\circ}$) = intercept of the plots $\log\{k_{1obs}(1 + [B]/[BH^+])\}$ vs. Mc (or $\log k_1^*$ vs. Mc).

The Mc function is a measure of the deviations from the ideality of the species involved in aqueous solutions of strong acids whose values can be experimentally estimated by following both the protonation of weak bases (equilibrium 1) and the dissociation of the acids themselves (equilibrium 5). In the latter case, the parameters of the acidic mixtures described by Eqs. (6) and (7) allow to obtain a Mc(s) function of the solvent defined by Eq. (8).

$$HA \rightleftharpoons H^+ + A^- \tag{5}$$

$$pK_{HA} = \log\left(\frac{[HA]}{[A^-]}\right) - \log[H^+] - \log\left(\frac{f_A - f_{H^+}}{f_{HA}}\right) \tag{6}$$

$$pK_{HA} = \log\left(\frac{[HA]}{[A^-]}\right) - \log[H^+] + Mc(s) \tag{7}$$

$$-\log\left(\frac{f_A - f_{H^+}}{f_{HA}}\right) = Mc(s) \tag{8}$$

The Mc(i) and Mc(s) functions, obtained respectively by the equilibria of solutes (i) and of solvents (s), are found to be linearly related (between them) by the relationships (9) or (9′).

$$-\log\left(\frac{f_B f_{H^+}}{f_{BH^+}}\right) = -n_{is} - \log\left(\frac{f_A - f_H}{f_{HA}}\right) \tag{9}$$

$$Mc(i) = n_{is}Mc(s) \tag{9'}$$

In the elucidation of the problems of acidity it has be shown that the n_{is} (or n_B) values are parameters related to the "protonating ability" of the acidic medium and can be interpreted as a measure of the specific interactions between solutes and solvents in the proton transfer process from $(H^+)_{aq}$ A^- to BH^+A^-. Such a procedure, already applied in equilibria [11–14] and reactivity [13,15,38,39] studies in different acid systems, allows one to obtain equilibrium constants and kinetic values referred to water as standard state, respectively. In Table 5 A the "$\log k_1^*$" rate constants for acetophenone obtained from the corresponding $\log k_{1obs}$ values by taking into account the equilibrium 1, are also reported. The new relationship of the reaction rate is related to the effective concentrations of the reacting species by Eq. (10), rewritten as (11), on the assumption that $[BH^+]$ is the electrophile.

$$\text{Rate} = k_{1obs}([B] + [BH^+])_{st} = k_1^*([BH^+])_{sol} \tag{10}$$

$$k_{1obs}\left(1 + \frac{[B]}{BH^+}\right) = k_1^* \tag{11}$$

Furthermore, the linear trend observed between "$\log k_1^*$" versus Mc allows one to obtain, by the intercept, the "$\log k_1^\circ$" rate constant referred to water as standard state. In the reaction between acetophenone and the nitrosating agent a value of $\log k_1^\circ = -0.3$ has been estimated.

An extension of the previous studies, using an analogous procedure, was also attempted by exploiting the available kinetic data estimated in the detritiation, iodination and bromination of acetophenone carried out in sulfuric, perchloric and hydrochloric acids [16–21]. The treatment of the experimental values by the described procedure shows that the $\log k_1^\circ$ constants, calculated from the literature data, are in agreement between them and with the $\log k_1^\circ$ obtained in the nitrosation of acetophenone. Thus, the new rate constant (k_1°) does not depend on the nature of the electrophile as well as on the acidity of the media.

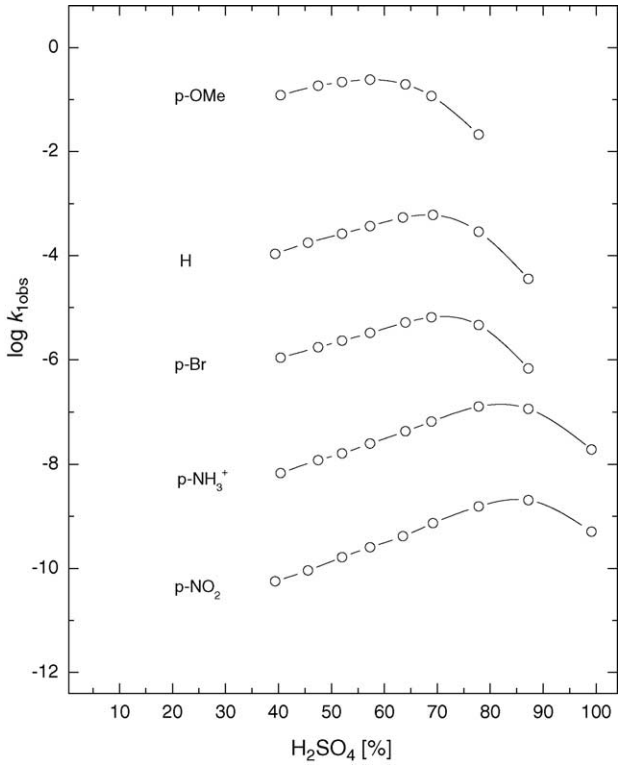


Fig. 1. Influences of H_2SO_4 concentration on detritiation of substituted acetophenones.

The validity of the results comes from the observations obtained in the detritiation of substituted acetophenones in sulfuric acid whose experimental $\log k_{1obs}$ values are reported in Fig. 1. Also in this case the corresponding "$\log k_1^*$" values by Eq. (11) and the "$\log k_1^\circ$" values by the plots "$\log k_1^*$" versus Mc, were estimated (Table 5 B). The linear relationship between thermodynamic rate constants ($\log k_1^\circ$) and equilibrium constants (pK_{BH^+}) reported in Fig. 2 clearly shows that the reaction under investigation proceeds through a common rate-determining step whose $\log k_1^\circ$ values are related, by the substituents effects, to the activation of the tritiated methyl group in α position to a carbonyl group.

3.3. Analysis of the intermediates

The kinetic studies of the reaction between acetophenone and the nitrosating agent in sulfuric acid essentially show

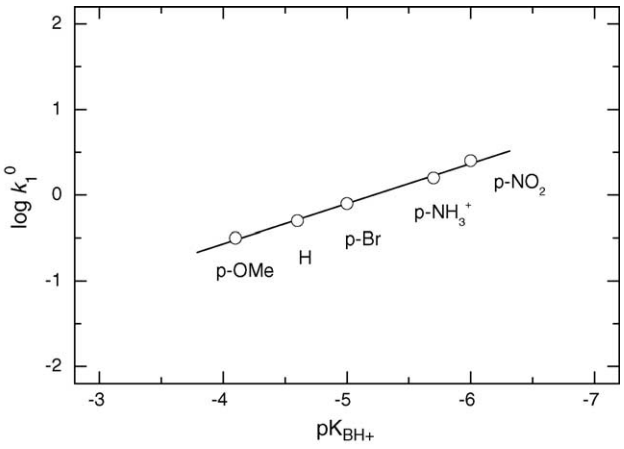


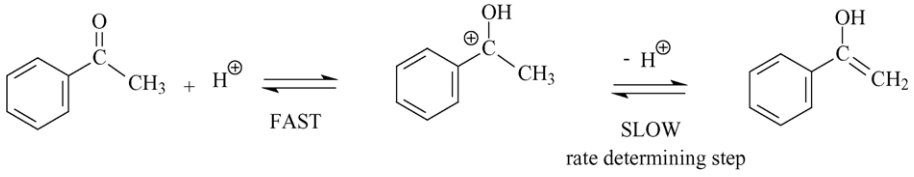
Fig. 2. Relationship between thermodynamic rate constants ($\log k_1^\circ$) and equilibrium constants (pK_{BH^+}) in detritiation of substituted acetophenones.

the involvement of ionic species and a rate-determining step described by Scheme 1.

Unfortunately, under these circumstances, further descriptions of the reaction progress to account for the formation of the products appear to be a matter for conjecture due to the uncertainty of the subsequent reaction pathways in acidic media of different strength.

On the attempt to obtain further details for the reaction, it seemed reasonable to follow the trend of the species α-nitroso-acetophenone and phenylglyoxal identified as intermediates, whose yields are decreasing as they were converted into the final products. Strong evidences that the reaction proceeds through the nitrous-compound are reported in Table 6, where the conversion of α-nitroso-acetophenone with and without NO^+ ion in H_2O and within different acidity ranges of sulfuric acid is tested. Practically, high yields of benzoylformic acid are observed under conditions analogous to that reported in Table 1.

The susceptibility of phenylglyoxal to oxidation and the conversion ArCOCOOH → ArCOOH as final step of the oxidation process are also given in Table 6. The results suggest that α-nitroso-acetophenone and phenylglyoxal give benzoylformic acid and/or benzoic acid in analogous experimental conditions. A likely sequence after the rate-determining step is summarised in Scheme 2 where it is

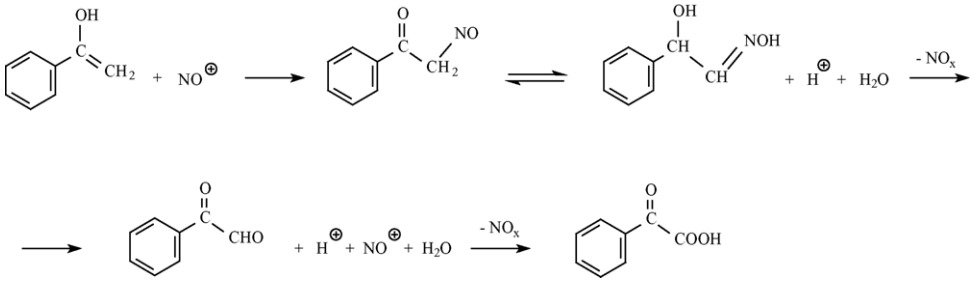


Scheme 1.

Table 6
Reactivity of α-nitroso-acetophenone, phenylglyoxal and benzoylformic acid in H_2SO_4 without and with nitrosating agents at 25 °C

Reagents[a]	H_2SO_4 (%)	Conversion[b] (%)	Yield %[b,c] ArCOCHO	Yield %[b,c] ArCOCOOH	Yield %[b,c] ArCOOH
α-NO-acetophenone	H_2O	–	–	–	–
α-NO-acetophenone (+$NaNO_2$)	H_2O	∼100	∼100	–	–
α-NO-acetophenone	52	2	∼1	∼0.1	∼0.1
α-NO-acetophenone (+NO^+)	52	99	∼1	35	45
α-NO-acetophenone	77	47	5	–	14
α-NO-acetophenone (+NO^+)	77	99	2	85	2.5
α-NO-acetophenone	96	99	∼0.1	∼0.1	98
α-NO-acetophenone (+NO^+)	96	99	∼0.1	∼0.1	99
Phenylglyoxal	52	–	∼100	–	–
Phenylglyoxal (+NO^+)	52	96	4	95	∼1
Phenylglyoxal	77	–	∼100	–	–
Phenylglyoxal (+NO^+)	77	99	∼1	95	∼1
Phenylglyoxal	96	90[d]	10	–	∼1
Phenylglyoxal (+NO^+)	96	99[d]	10	–	30
Benzoylformic acid	80	–	–	∼100	–
Benzoylformic acid (+NO^+)	80	–	–	∼100	–
Benzoylformic acid	85	3	–	–	3
Benzoylformic acid (+NO^+)	85	1	–	–	1
Benzoylformic acid	90	43	–	–	43
Benzoylformic acid (+NO^+)	90	26	–	–	26
Benzoylformic acid	96	∼99	–	–	∼99
Benzoylformic acid (+NO^+)	96	∼99	–	–	∼99

[a] Ratio reagents:oxidant = 1:4.
[b] Conversion and yields of products after 24 h analysed by HPLC.
[c] Yields of identified products.
[d] Pitchy material.



Scheme 2.

shown one of the most probable route, which accounts for the intermediates that have been analysed.

It is suggested that: (a) phenylglyoxal is formed by protonation and hydrolysis of benzoylformaldehyde oxime, tautomeric form of α-nitroso-acetophenone; (b) benzoylformic acid is formed by the subsequent processes involving protonation, attack of nitrosonium ion and hydrolysis of phenylglyoxal. Obviously, alternative routes by α-dinitroso- and α-trinitroso-acetophenones cannot be ruled out.

4. Conclusions

From a practical point of view the results show that the selective oxidation of acetophenone and cycloexanone by a nitrosating agent in acidic media can be of interest for synthetic applications. The observed experimental trend also suggests the utilization of two main experimental conditions: (i) an excess of the electrophilic species to ensure high conversions and yields; (ii) suitable acidity ranges of the acidic mixtures in order to obtain, by protonation–enolization, activated reacting species of ketones. High acidity ranges leads to further oxidative processes of the products already formed, or strong interactions between reagents and solvent. For instance, the low conversion of acetophenone observed in H_2SO_4 with concentration above 80% (Table 1) suggests that in this range the involvement of $HSO_4^-{\cdot}[PhC(OH)CH_3]^+$ ion-pair decreases the efficiency of the reacting species [14,15,38]. An earlier report also shows that iodination of acetophenone is highly reversible in 95% H_2SO_4 [16]. The conversion benzoylformic acid to benzoic acid above 90% H_2SO_4 (Table 6) suggests, in this acidity range, the involvement of other protonation equilibria suitable to give a more stable compound by a decarboxylation reaction.

Conversion of cyclohexanone increases with increasing the acid concentration but the formation of 1,2-cyclohexanedione (maximum yield 58%) is achieved under suitable experimental conditions (40% H_2SO_4; cyclohexanone:$NaNO_2$ = 1:4) where the next steps of oxidation of the cyclic α-diketone can be minimized.

An extension of these studies over solid acid materials will be reported in a subsequent paper (part 2) on the attempt to replace homogeneous acid systems, in order to avoid some practical and environmental problems of acid-catalysed reactions carried out in concentrated aqueous solutions of strong acids.

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